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Theoretical Investigations for the Behavior of Hydrotropes in Aqueous Solution

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Abstract: The presented paper introduces an attempt for finding a theoretical model capable for describing the critical aggregation concentration (cac) for some hydrotropes (a series of sodium-p-n-alkylbenzoates, n=0-8). Such a proposal was carried out through theoretical calculations based on density functional theory (DFT) for estimating some physical properties which might be helpful for supporting the recent published report as all of these hydrotropes are considered as surfactant like (see doi: 10.1021/la2025846). The estimated physical properties can be divided to three classes according to their effect: steric properties such as volume and surface area, electronic properties such as polarizability, and hydrophobic properties such as log P which represents the ratio of concentrations of a compound in two phases of octanol and water. The results show that both steric and hydrophobic properties play major roles in predicting the cac for the presented hydrotropes. The best model was found between cac and tail polarizability (PT) according to the following relation: cac = 1.52-1.09log PT ; with r^2 equal to 0.96, S.E equal to 0.026 M and significant cross validation correlation coefficient (0.943). A unique feature of the presented model is containing only one descriptor with excellent statistical parameters. This actually supports the recent (above mentioned) published results of that all of these hydrotropes can be considered as surfactant-like. The suggested models were applied to some randomly selected surfactants with reasonable results. The results are generally suggesting for the possibility of estimating the cac or critical micelle concentration (cmc) for amphiphilic molecules using computational chemistry software.
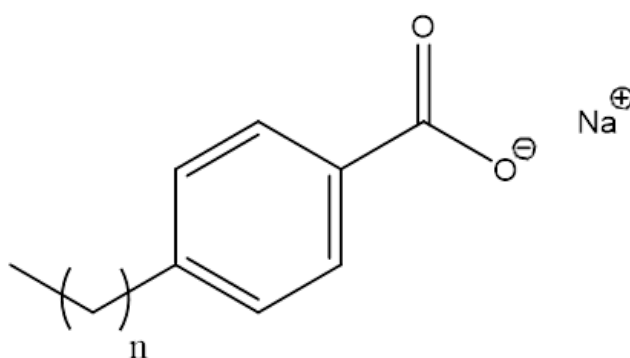
■ Introduction

In recent years, hydrotropes as amphiphilic organic molecules has long been a special topic due to their special characteristics, giving the possibility for their employment in many aspects [1, 2]. However, a clear and general definition of hydrotropes still need verification [3,4]. For instance, hydrotropes are divided into two classes from self-assembly point of view; surfactant-like and unlike. In other words, the chain length of hydrophobic part of hydrotrope plays the major role on the last classification. Recently, Hopkins Hatzopoulos et al.[5] investigated the physicochemical properties of a homologous series of sodium p-n-alkylbenzoates (Scheme 1). They stated according to their results of small angle neutron scattering (SANS) technique and surface tension analysis that all of these hydrotropes display as surfactant like behaviors with no regard to the chain length. Subsequently, they have supported this event through studying the effects of structure variation on physicochemical behavior of hydrotropes composed of sodium phenyl-n-alkanoates and cyclohexyl-n-alkanoates [6].

Actually, such a surprising phenomenon was attracted us for theoretical verification using quantum mechanical calculations. According to the literature, there is no theoretical study based on quantum mechanical methods that have been performed for hydrotropes. Such kind of a study was only found for surfactant molecules. For instance, Huibers studied the electrical charge distribution in some ionic surfactants using quantum chemical calculations [7]. He indicated that the partial charge distribution influences surfactant self-assembly and physical properties. Other publications based on employing the quantitative structure-property relationship (QSPR) have been found for a considerable number of anionic surfactants [7-14]. A part of complexity for the prediction of descriptors has been mostly shown by these investigations. For examples, the Kier and Hall descriptor was calculated indirectly through many parameters [13].

Scheme 1. Chemical structure of sodium p-n-alkylbenzoates; n=0-8.

Thus, the presented paper introduces theoretical investigations using density functional theory (DFT) and qualitative structure property relationship (QSPR) calculations that might be helpful for understanding the recent published results of hydrotropes [5]. It should be noted that we have recently used these hydrotropes to develop a theoretical model that used for evaluating the critical packing parameter of self-assembled amphiphilic molecules [15]. The obtained results were indirectly supporting that the members of all studied hydrotropes family may be considered as surfactant-like.

■ Theoretical section

The experimental cac values of used hydrotropes (sodium p-n-alkylbenzoates, n=0-8) were taken from Reference 5. The experimental cmc of all selected surfactants were taken from Reference 16.The chemical structural inputs for of all presented molecules and their models were prepared by using HyperChem 8.0.8 program package. Each of the structures was employed as a starting point for energy minimization using molecular mechanics MM2, semi-empirical PM3 and DFT methods according to our developed procedure that has already listed in the related published research [15]. In this method, a series of computational operations have been suggested in order to reach the best method from accuracy and time-consuming points of views. In other words, our treatments deal with relatively huge molecules (surfactants) which need long periods of time if one uses large or medium basis set for computation process. Therefore, considerable efforts have been paid in order to find an accurate method using small basis set. It has been found that the use of molecular mechanics for a conformational analysis and then a geometric optimization with DFT at relatively small basis set (3-21G) and B3LYP hybrid functional is a significant tool to search for the global minima [15].

This procedure eliminates the significance of using large and medium basis sets which therefore the time consumed for this process is comparatively very short. The selected properties of the presented molecules were estimated from their optimized structures Finally, Minitab program (MINITAB Release 14.1, www.minitab.com) was used for regression analysis of the calculated data.

■ Results and discussion

The recent observation by Hopkins Hatzopoulos et al. [5] with respect to SANS analysis showed that all hydrotropes (sodium p-n-alkylbenzoates, n=0-8) behaving as surfactant-like which has guided us to do theoretical investigations which might be helpful in illustrating such a phenomenon. In fact, the latter observation contradicts with the well-known assumption of that surfactant molecules must have chain of at least 8 carbon atoms in order to have self-assembled structure or following an "on-off" mode of aggregation. Table 1 lists the calculated theoretical parameters using DFT method for the presented compounds.

The results show no remarkable difference in head charge, tail charge, head surface area, charge on α-CH_2, polarizability of head, HOMO, LUMO for these hydrotropes. The reason for this may be attributed to the relatively low reactive side of the hydrocarbonic alkyl chain as saturated group in contrast to the head group which remains fixed for all of the presented hydrotropes. In other words, these parameters have no influence on the cac values of amphiphilic molecules. It is clearly shown (Table 1) the head volume increased in zigzag mode with increasing the tail length. Such non-linear mode which represents the charge of number of methylene groups from odd to even is not new here. This is due to the observation that the zigzag mode was already found for some physical properties of hydrocarbons particularly those of alkynes. However, the increase in head volume may be attributed to that the negative charge of the head is enhanced by increasing the number of CH_2 groups as considered as electron donor group. On the other hand, the results indicate that the Log P values which represent the ratio of concentrations of a compound in the two phases of a mixture of two immiscible solvents at equilibrium "octanol and water" increases with increasing tail length. For instance, compounds with high partition coefficients (high Log P) are preferentially distributed to hydrophobic compartment while hydrophilic compounds (low Log P) are preferentially found in the hydrophilic part. This can be attributed to the hydrophobic interactions through dispersion forces. On the other hand, the polarizability (α) was also increased with the increasing the number of CH_2 groups at the tail because α depends on the induced dipole moment which is increased with increasing number of CH_2 groups according to the following relation [17], where (μ_{ind}) is the induced dipole moment and (E) is the electric field strength.

$$\alpha = \mu_{ind} / E \ (C^2 \ m^2 \ J^{-1})$$

$$(1)$$

Table 1. List of the calculated properties of the sodium p-n-alkylbenzoates (n=0-8) hydrotropes.

Property	Sodium p-n-alkylbenzoate (n=0-8) hydrotropes								
	n = 0	n = 1	n = 2	n = 3	n = 4	n = 5	n = 6	n = 7	n = 8
Head Charge (e)	-0.765	-0.768	-0.768	-0.767	-0.765	-0.767	-0.764	-0.767	-0.765
Tail Charge (e)	-0.338	-0.336	-0.340	-0.337	-0.339	-0.337	-0.339	-0.337	-0.337
Charge α-CH_2 (e)	non	-0.232	-0.224	-0.202	-0.206	-0.201	-0.206	-0.202	-0.206
Head Surface area $A^{\circ 2}$	93.29	93.53	92.77	93.01	93.45	93.89	93.60	94.06	93.89
Tail surface area $A^{\circ 2}$	181.48	213.28	240.49	269.73	303.02	331.38	366.79	395.39	427.66
Total surface area $A^{\circ 2}$	274.77	301.82	328.13	357.89	392.11	420.22	456.62	484.38	517.21
Head Volume $A^{\circ 3}$	947.8	1110.2	1098.5	1173.0	1135.3	1326.5	1404.5	1478.7	1322.5
Tail volume $A^{\circ 3}$	358.50	473.64	517.32	578.54	630.41	690.71	740.06	792.38	820.95
Total volume $A^{\circ 3}$	396.98	449.49	498.77	553.21	611.61	663.10	719.40	772.33	828.84
Chain length A°	3.50	5.02	6.10	10.46	8.62	10.00	11.20	12.56	13.76
Log P Tail	1.706	2.333	2.729	3.125	3.522	3.918	4.314	4.711	5.107
Log P Total	3.166	3.633	4.030	4.426	4.822	5.218	5.615	6.011	6.407
Polarizability of Head/ $C^2 m^2 J^{-1}$	3.842	3.842	3.842	3.842	3.842	3.842	3.842	3.842	3.842
Polarizability ofTail/ $C^2 m^2 J^{-1}$	8.695	11.882	13.717	15.552	17.387	19.222	21.057	22.892	24.727
Total polarizability $C^2 m^2 J^{-1}$	12.54	14.37	16.21	18.04	19.88	21.71	23.55	25.38	27.22
HOMO (eV)	-4.62	-4.62	-4.62	-4.63	-4.65	-4.64	-4.66	-4.64	-4.66
LUMO (eV)	3.93	3.84	3.84	3.83	3.77	3.81	3.75	3.80	3.74
[cac] [5]	0.480	0.320	0.300	0.280	0.200	0.090	0.048	0.024	0.011

In order to find the best relationship between the calculated values of physical properties with the practical values of cac (Table 1), a general correlation matrix which gathers all calculated properties has been formed. Indeed, such a matrix will be quite helpful in order to verify if there is any combination between the calculated parameters. For example, the property of refractivity is derived directly from the polarizability which was therefore neglected from Table 1. This can be considered as an important point while concerning with building a multi-parametrical model. Interestingly, the results of constructed matrix show according to statistical parameters there is only one descriptor which is quite enough for predicting the cac of the presented hydrotropes as exhibited in Table 2. Indeed, this gives an efficient support to the previous experimental results [5, 6] as all the investigated sodium salts hydrotropes possess 'on-off" mode of association with no regards to hydrophobic chain length. This event may be explained in terms of the phenomenon that the presence of sodium carboxylate group as a polar head which could acts as an anti-hydrophobic effect. In other words, the water molecules surrounding this polar group will decrease the hydrogen bonding between each other which then reduce the density of solution [18]. Then, the movement of hydrotropes within solution will be much easier in this state as the shorter hydrophobic chain length will be more efficient in contrast to that of longer. This is because of the fact that the neighboring water molecules will be relatively close to hydrophobic part of shorter chain, while, the hydrophobic interactions of the longer chain length play the major role for aggregation. Thus, all of these hydrotropes behave as surfactant-like.

Hence, four properties have been chosen as a single descriptor for each developed model possessing good statistics stability and predictive power. One of these properties represents the electronic effect (polarizability of tail) and two representing the steric effect (tail volume and tail surface area). While the last one (log P of tail) is considered as a measure of the amount hydrophobicity which increases with increasing tail length (number of CH_2 groups) as illustrated above. Moreover, this parameter can be considered as hydrophilic-lipophilic balance of a substance which reflects its partitioning behavior between a polar (water) and non-polar (oil) medium. In fact, there is a clear physical meaning realized from all of these equations as the cac decreases with increasing the number of $-CH_2$-group. It should be noted that all of above selected descriptors are representing the properties of the hydrophobic group (tail) which is in good agreement with theory of micellization.

The results show that the amounts of the intercepts are more than the cac of the shorter chain length which give an indication for the successfulness of all suggested models. On the other hand, the relationship between the experimental and calculated cac values for these four models (Table 2) signifies an apparent weak point that resulted from the negative values of cac for the longer alkyl chain length (lower cac value), as shown clearly in Figure 1. Indeed, such a problem can be also realized from the value of standard error for the above model which exceeds the value of cac for the lower cac molecule. Therefore, the investigations should be extended for another suitable model. Such a problem may suggest there is no perfect linearity between cac versus the selected physical properties. Therefore, the relationship should be improved through using some mathematical operators such as square root, log, exponential, and so on. The results of such curve fitting treatments indicate that the logarithmic operator is the proper one which gives the best statistical stability and predictive power for the three properties TVO, PT and LPT as illustrated in Table 3.

Furthermore, the latter curve-fitting process has solved the problem of the negative value for those best three models as shown clearly in Figures 2-4. The parameters of cross validation correlation coefficient (q^2) and standard deviation of residual between observed and calculated values of cac have been introduced (Table 3) due to the apparent closeness in the values of statistical parameters (r and S.E.) of these models. Indeed, the values of q^2 for these models are quite close to each other which they near to the top value (unity). However, the best model may be chosen with respect to the relatively best value of standard deviation between observed and fitted cac as given in Table 3. Hence, the model of polarizability of tail ([cac] = 1.52-1.09 log PT) is considered as the most powerful model for estimating the cac of the presented hydrotropes. In general, this model is quite significant from both of physical and statistical point of views.

Table 2. The best selected models obtained from the correlation matrix between cac and some of the calculated theoretical properties of hydrotropes with statistical parameters.

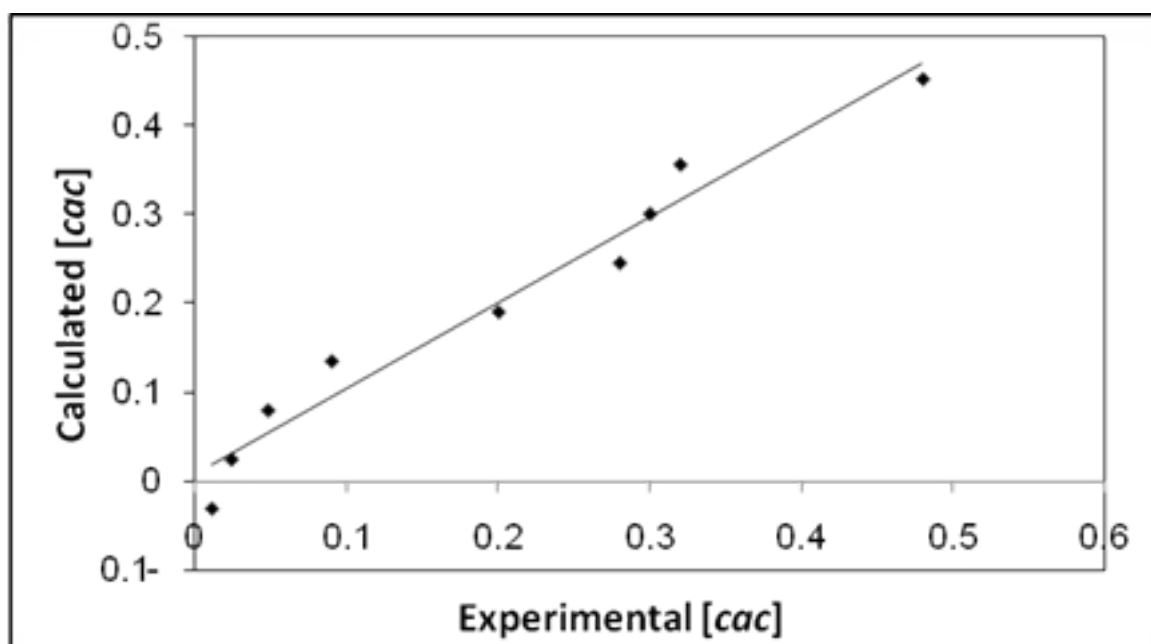| Property	Symbol	Model (y=a-bx)	r	S.E. (M)
Tail volume	TVO	[cac] = 0.840 −1.04x10^{-3}TVO	-0.988	0.032
Tail surface area	TSA	[cac] = 0.763 - 1.97x10^{-3}TSA	-0.972	0.040
Polarizability of tail	PT	[cac] = 0.714 −3.01x10^{-2}PT	-0.980	0.034
Log P of tail	LPT	[cac] = 0.687 - 0.141 LPT	-0.979	0.035

Figure 1. The relationship between experimental cac values and predicted cac of polarizability of tail (PT).

Table 3. The best selected models obtained from the treatment by curve-fitting for the relation between cac and some of the calculated theoretical properties of hydrotropes with statistical parameters.

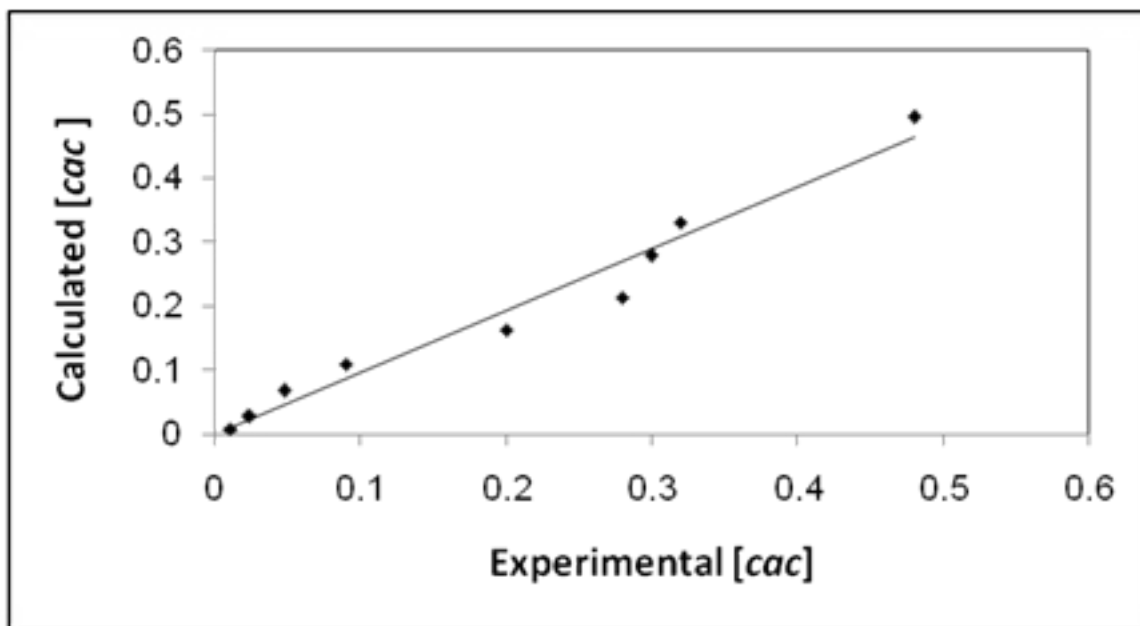| Property	Symbol	Model	r	S.E. (M)	q^2	SD (M)
Tail volume	TVO	[cac] = 3.97-1.36 logTVO	-0.983	0.033	0.945	0.088
Polarizability of tail	PT	[cac] = 1.52-1.09 log PT	-0.981	0.033	0.943	0.026
Log P of tail	LPT	[cac] = 0.730-1.03 logLPT	-0.981	0.034	0.945	0.039

Figure 2. Relationship between experimental cac and calculated cac values from the logarithm of tail volume.
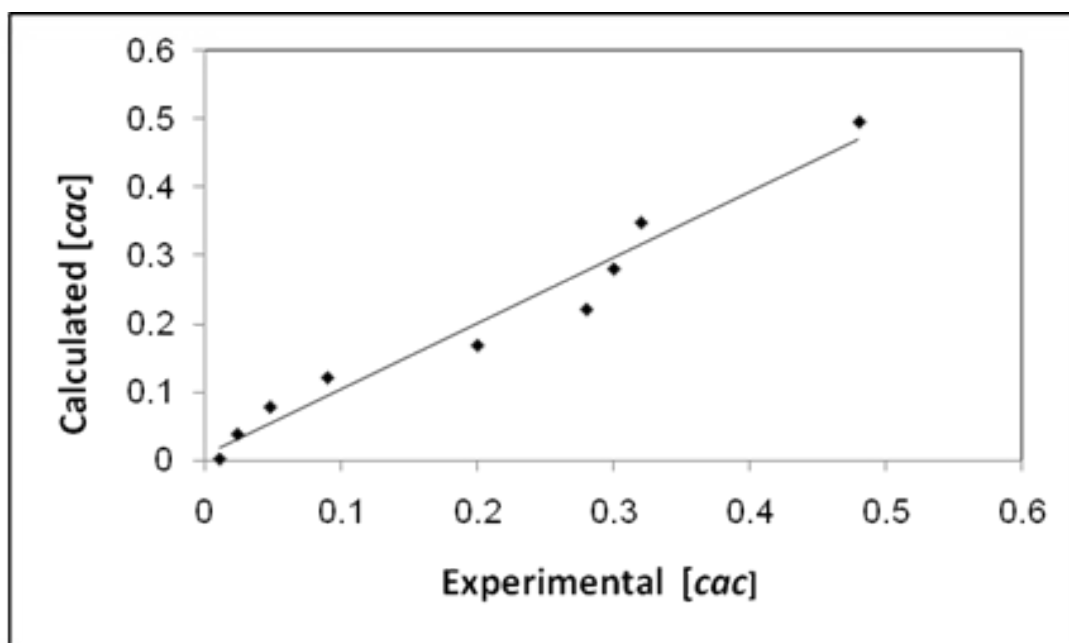

Figure 3. Relationship between experimental cac and calculated cac values from the logarithm of polarizability of tail.
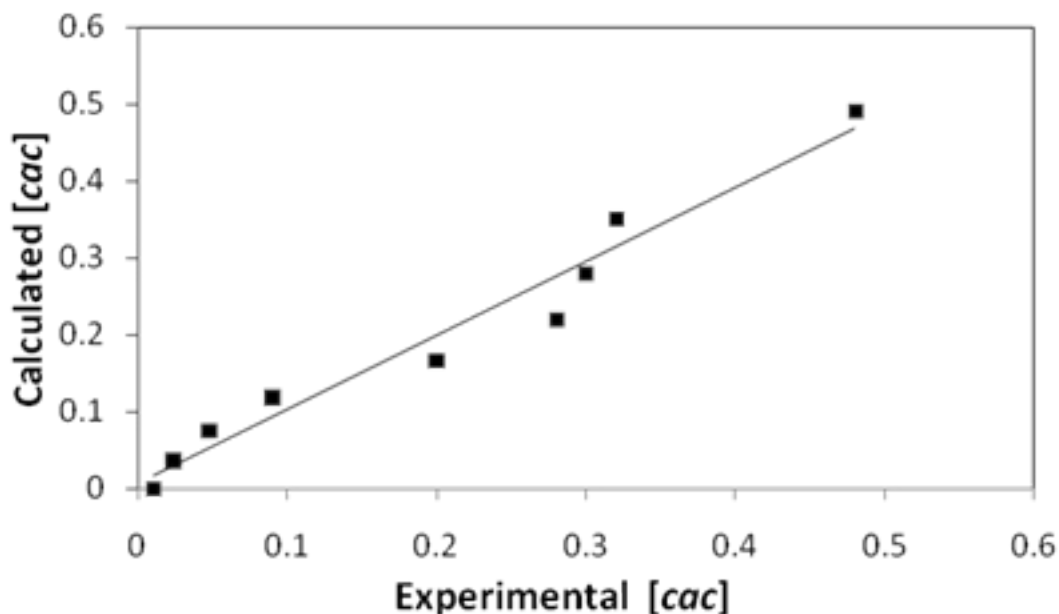
Figure 4. Relationship between experimental cac and calculated cac values from the logarithm of Log P of tail.

An application of the above selected three models for predicting critical micelle concentration (cmc) of two sets of different head groups of anionic surfactants was carried out as illustrated in Table 4. It is not surprising that the presented models are not applicable for estimating the cmc of ionic surfactants in contrast to cac of hydrotropes [19]. This can be attributed to the effect of presence of free gegen- or counter-ions which not exciting in hydrotropes systems. Furthermore, the presence of free gegen-ions could disturb the interactions between head groups which therefore deform the symmetry of micelle or aggregate system. Actually, the presence of these ions at Gouy-Ghapman layer [20] creates a real problem in computational investigations. This because the theoretical calculations estimate the properties of surfactant molecules in its monomer state as all these molecules are the same when they accumulated in micelle structure. It is apparent that the presented models are relatively more applicable for determining the cmc of sodium acetate micelle in contrast to that of sodium sulfate according to the values of statistical parameters as clearly shown in Table 4. This is because of the fact that the amount of free gegen-ions depends on the ionization of surfactant molecule. The relatively low ionization potential of sodium acetate surfactant decreases the probability of the presence of free gegen-ions in contrast to that of sodium sulfate. However, the values of standard deviation again suggest that the model of tail polarizability is relatively the best model for estimating the cmc of surfactants.

Table 4. Predicted *cmc* for some surfactants using the three models of Table 3 versus experimental *cmc*.

Surfactant	*cmc*[a] [M]	TVO (A^{-3}) {*cmc*}[b] (Δ)[c]	PT(C^2 m^2 J^{-1}) {*cmc*}[d] (Δ)[c]	LPT {*cmc*}[e] (Δ)[c]
Sodium tatradecylsulfate	0.0021	1125.961 {-0.1800} (-0.1821)	27.912 {-0.0559} (-0.058)	5.487 {-0.0315} (-0.0336)
Sodium dodecylsulfate	0.0083	968.739 {-0.0912} (-0.0995)	22.407 {0.0480} (0.0397)	4.298 {0.0777} (0.0694)
Sodium decylsulfate	0.0330	860.835 {-0.0214} (-0.0544)	18.737 {0.1327} (0.0997)	3.506 {0.1688} (0.1358)
Sodium octylsulfate	0.1330	752.695 {0.0577} (-0.0753)	15.067 {0.2359} (0.1029)	2.713 {0.2835} (0.1505)
SD[f]		0.103	0.075	0.097
r^2		0.77	0.79	0.80
Sodium octanoate	0.4000	609.929 {0.1820} (0.2180)	13.232 {0.2974} (-0.1026)	2.562 {0.3091} (-0.0909)
Sodium nonanoate	0.2100	667.713 {0.1285} (-0.0815)	16.419 {0.1952} (-0.0148)	3.030 {0.2341} (0.0241)
Sodium decanoate	0.1090	721.698 {0.0826} (-0.0264)	18.254 {0.1451} (0.0361)	3.426 {0.1791} (0.0701)
Sodium dodecanoate	0.0278	828.746 {0.0009} (-0.0269)	21.924 {0.0583} (0.0305)	4.218 0.0861 (0.0583)
SD		0.088	0.046	0.061
r^2		0.91	0.98	0.94

[a] Experimental *cmc* taken from Ref. 16, [b] calculated using this Eq. [*cac*] = 3.97-1.36 logTVO, [c] Δ= *cmc* (calculated,) − *cmc* (experimental), [d] calculated using this Eq. [*cac*] = 1.52-1.09 log PT, [e] calculated using this Eq. [*cac*] = 0.730-1.03 logLPT, [f] Standard deviation.

■ Conclusions

On the basis of our results, one could conclude that there are good models which are statistically significant have been developed for estimating the cac of hydrotropes. In addition, the obtained results have supported the recent reports of Hatzopoulos et al. [5, 6] reflecting that all hydrotropes could act as a surfactant. It is not possible to apply a unique model for all kinds of hydrotropes and surfactants due to the change in the head group interactions in addition to gegen-ions effect. The results suggest that the estimation of cac or cmc for amphiphilic molecules using computational chemistry tools is quite possible. Finally, theoretical calculations based on density functional theory can be considered as a powerful tool for estimation the physical properties of amphiphilic molecules.

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